JC02 Rec'd PCT/PTO 29 MAR 2002

FORM PTO-1390 (REV. 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
3868-0113P	10/089944 NEW

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/09061	September 16, 2000	September 30, 1999

TITLE OF INVENTION
PREPARATION CONTAINING ACTIVE AND/OR AUXILIARY SUBSTANCES, WITH CONTROLLABLE RELEASE OF SAID SUBSTANCES, AS WELL AS ITS USE AND MANUFACTURE

APPLICANT(S) FOR DO/EO/US
VON FALKENHAUSEN, Christian and KRUMME, Markus

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is transmitted herewith.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4)
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☒ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 20. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98, Form PTO-1449(s), and International Search Report (PCT/ISA/210) with 0 document(s).
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information:
    1.) PCT Substitute Claims Letter w/PCT/IPEA/416, PCT/IPEA/409, amended claims and translation thereof.
    2.) Five (5) sheets of formal drawings

JC10 Rec'd PCT/PTO 29 MAR 2002

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
NEW 10/089444	PCT/EP00/09061	3868-0113P

21. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. **$1,040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO. **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4). **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	23 - 20 =	3	X **$18.00**	$ 54.00	
Independent Claims	5 - 3 =	2	X **$84.00**	$ 168.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)		NO	+ **$280.00**	$ 0.00	
			TOTAL OF ABOVE CALCULATIONS =	$ 1242.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$ 0.00	
			SUBTOTAL =	$ 1242.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0.00	
			TOTAL NATIONAL FEE =	$ 1242.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 0.00	
			TOTAL FEES ENCLOSED =	$ 1242.00	
			Amount to be: refunded	$	
			charged	$	

a. ☒ A check in the amount of $ **1242.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account. No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to:
Birch, Stewart, Kolasch & Birch, LLP or Customer No. 2292
P.O. Box 747
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Date: March 29, 2002

Reg No

By Joe M. Mung 32,387
for James M. Slattery, #28,380

/ka

PATENT
3868-0113P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	VON FALKENHAUSEN, Christian et al		
Int'l. Appl. No.:	PCT/EP00/09061		
Appl. No.:	NEW	Group:	
Filed:	March 29, 2002	Examiner:	
For:	PREPARATION CONTAINING ACTIVE AND/OR AUXILIARY SUBSTANCES, WITH CONTROLLABLE RELEASE OF SAID SUBSTANCES, AS WELL AS ITS USE AND MANUFACTURE		

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington, DC 20231

March 29, 2002

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

AMENDMENTS

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/EP00/09061 which has an International filing date of September 16, 2000, which designated the United States of America.--

Docket No. 3868-0113P

IN THE CLAIMS:

Please amend the claims as follows:

3. (Amended) Preparation according to Claim 1, characterized in that it comprises at least one continuous and substantially moisture-impermeable layer.

5. (Amended) Preparation according to Claim 1, characterized in that at least one of the layers (2) of the laminate is soluble or erodible in body fluid, and another layer (1) is less readily soluble or more difficult to erode, or is even insoluble or non-erodible.

6. (Amended) Preparation according to Claim 1, characterized in that the concentration of the active substance or of the active substances varies in respect of the longitudinal extension of the active substance-containing layer(s), preferably in the form of a concentration gradient or an otherwise variable concentration profile.

7. (Amended) Preparation according to Claim 1, characterized in that at least one layer, in particular the matrix (2), is pressure-sensitive adhesive.

8. (Amended) Preparation according to Claim 1, characterized in that in the spirally rolled-up laminate the outer layer (2) contains active and/or auxiliary substances.

9. (Amended) Preparation according to Claim 1, characterized in that in the spirally rolled-up laminate the inner layer (2) contains active and/or auxiliary substances.

10. (Amended) Preparation according to Claim 1, characterized in that one layer has regions with active and/or auxiliary substances, which regions differ in terms of their solubility, adhesive power or erosion properties.

11. (Amended) Preparation according to Claim 1, characterized in that if it is configured in form of a winding, it comprises a winding core which consists of material which is optionally soluble or insoluble in body fluid.

12. (Amended) Preparation according to Claim 1, characterized in that in the center of the winding there is formed a tube-like recess of at least 0.5 mm in diameter.

13. (Amended) Preparation according to Claim 1, characterized in that the preparation effects a linear release of active substance.

14. (Amended) Preparation according to Claim 1, characterized in that the preparation effects the release of an initial dose.

15. (Amended) Preparation according to Claim 1, characterized in that those sides of the spirally rolled-up or folded preparation which correspond to the longitudinal sides of the respective layers are provided with additional cover layers, said cover layers preferably containing substantially moisture-impermeable materials.

16. (Amended) Preparation according to Claim 1, characterized in that the preparation is embedded in a substrate (5) which preferably consists of a substance that is soluble in acidic or basic environment.

22. (Amended) Process according to Claim 20, characterized in that further active layers (3, 4) are laminated to the laminate.

23. (Amended) Process according to Claim 20, characterized in that the preparation is embedded in a substrate (5).

Docket No. 3868-0113P

REMARKS

The specification has been amended to provide a cross-reference to the previously filed International Application.

The amendment to the claims is merely to delete multiple dependencies and to place the application into better form for examination.

Entry of the above amendments is earnestly solicited. An early and favorable first action on the merits is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the application by this Amendment.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By [signature] Reg No. 32,334
James M. Slattery, #28,380

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JMS/ka
3868-0113P

Attachment: VERSION WITH MARKINGS TO SHOW CHANGES MADE

(Rev. 02/21/02)

Docket No. 3868-0113P

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The claims have been amended as follows:

3. (Amended) Preparation according to Claim 1 [or 2], characterized in that it comprises at least one continuous and substantially moisture-impermeable layer.

5. (Amended) Preparation according to [one or more of the preceding Claims] Claim 1, characterized in that at least one of the layers (2) of the laminate is soluble or erodible in body fluid, and another layer (1) is less readily soluble or more difficult to erode, or is even insoluble or non-erodible.

6. (Amended) Preparation according to [one or more of the preceding claims] Claim 1, characterized in that the concentration of the active substance or of the active substances varies in respect of the longitudinal extension of the active substance-containing layer(s), preferably in the form of a concentration gradient or an otherwise variable concentration profile.

7. (Amended) Preparation according to [one or more of the preceding claims] Claim 1, characterized in that at least one layer, in particular the matrix (2), is pressure-sensitive adhesive.

8. (Amended) Preparation according to [one or more of the preceding claims] Claim 1, characterized in that in the spirally rolled-up laminate the outer layer (2) contains active and/or auxiliary substances.

9. (Amended) Preparation according to [one or more of claims 1 to 7] Claim 1, characterized in that in the spirally rolled-up laminate the inner layer (2) contains active and/or auxiliary substances.

10. (Amended) Preparation according to [one or more of the preceding claims] Claim 1, characterized in that one layer has regions with active and/or auxiliary substances, which regions differ in terms of their solubility, adhesive power or erosion properties.

11. (Amended) Preparation according to [one or more of the preceding claims] Claim 1, characterized in that if it is configured in form of a winding, it comprises a winding core which consists of material which is optionally soluble or insoluble in body fluid.

12. (Amended) Preparation according to [one or more of the preceding claims] Claim 1, characterized in that in the [centre] center of the winding there is formed a tube-like recess of at least 0.5 mm in diameter.

13. (Amended) Preparation according to [one or more of the preceding claims] Claim 1, characterized in that the preparation effects a linear release of active substance.

14. (Amended) Preparation according to [one or more of claims 1 to 12] Claim 1, characterized in that the preparation effects the release of an initial dose.

15. (Amended) Preparation according to [one or more of the preceding claims] Claim 1, characterized in that those sides of the spirally rolled-up or folded preparation which correspond to the longitudinal sides of the respective layers are provided with additional cover layers, said cover layers preferably containing substantially moisture-impermeable materials.

16. (Amended) Preparation according to [one or more of the preceding claims] Claim 1, characterized in that the preparation is embedded in a substrate (5) which preferably consists of a substance that is soluble in acidic or basic environment.

22. (Amended) Process according to Claim 20 [or 21], characterized in that further active layers (3, 4) are laminated to the laminate.

23. (Amended) Process according to [one or more of Claims 20 to 22] Claim 20, characterized in that the preparation is embedded in a substrate (5).

Preparation containing active and/or auxiliary substances, with controllable release of said substances, as well as its use and manufacture

This invention relates to preparations containing active and/or auxiliary substances, for time- and/or dose-controllable release of said substances, said preparations containing at least two layers in rolled or folded form.

Active substance-containing preparations of whatever administration form generally release the active substance by diffusion or disintegration, which as a rule results in non-linear release kinetics. Embodiments of such systems can be applied as oral, rectal or vaginal administration forms, or if required also as implants.
Here, a demand frequently placed on the application form is the linear release of active substance from the preparation. However, it may also be desirable to freely modulate the release profile in correspondence with the specific demands placed on a therapeutic form. Preparations for such controlled, for example linear, active substance release are mostly of a complicated structure and are expensive in manufacture.

From the state of the art are known a number of active- and auxiliary substance-containing preparations, in particular with retarded release of the ingredients.
DE 43 41 442 describes an oral administration form consisting of a central, active substance-containing, non-erodible layer and a further, largely active substance-free, erodible layer enveloping said layer. Active substance release takes place by passive diffusion from the central layer, the latter being exposed to the release medium with a defined area. The reduction in the amount of active substance released per unit time is compensated by

the active substance that is additionally released from the coat layer as a consequence of erosion. The principle of providing new, "undepleted" surfaces by means of erosion of largely active substance-free cover layers enables extensive modulation of the release kinetics by means of targeted selection of core and coat layer geometries. The core of the invention of the aforementioned documents thus comprises the successive provision of new surfaces of active substance-containing layers.

US 3,625,214 describes a planar, helical, rolled-up administration form comprising two layers; the outward-facing layer being an active substance-free film which is soluble in water but is impermeable and which is coated with a water-soluble and active substance-containing matrix which is rolled inwardly, and said matrix possibly possessing a thickness profile along its extension. When this administration form is exposed to a body fluid, the outer layer erodes or dissolves and consequently exposes active substance-containing matrix material. This dissolves in the body fluid and thereby releases active agent. As a consequence of the helical winding, internal areas are exposed with delay which results in a retarded release of active substance, which release, due to varying thicknesses of the active substance-containing matrix, may have dose-modulated characteristics. Thus, the control of active substance release is accomplished here in terms of time by the exposure of new surfaces, and in terms of the dose by different thicknesses of the active agent-carrying layer.

DE 197 15 794 C1 describes a laminar drug form and a process for its manufacture. The invention for controlled active agent release comprises helically rolled-up, or folded layers on a polymer film which contains a pharmaceutically active agent. The invention is characterized in

that the outer surface of the active substance-containing polymer film, which surface is accessible to the digestive juices, in the rolled-up or folded state accounts for at most 25% of its total surface area, and the rolled-up or folded layers stick to one another such that in the release test according to USP 23, Method A, Apparatus 2, at 37 °C and 50 rpm, the laminar medicament form retains its spirally coiled or folded shape in synthetic gastric juice for at least one hour, and at least 30% of the contained active substance is released in the rolled-up or folded state.

US 4,767,627 describes an active substance delivery preparation with extended retention time in the stomach comprising a planar figure of an erodible polymer which releases an active substance contained therein over a controlled, predictable and extended period of time.

US 4,268,497 describes a preparation for oral administration in veterinary medicine containing a medicament in an erodible film. Said film has a first shape enabling oral administration, and a second shape in the stomach, causing its retention.

Starting from the aforementioned state of the art, it is the object of the present invention to provide an application form for an active substance-containing preparation which is less complicated in manufacture and enables a freely modulatable release with simple as well as inexpensive means.

To achieve this object it is proposed according to the present invention, for a preparation possessing the features mentioned in the introductory part of the main claim to contain at least one active or auxiliary substance in the first layer, and that said layer is continuous at

least in sections thereof, and that at least one of the parameters thickness, width and concentration of the active or auxiliary substance of this layer is not constant. In addition, the preparations according to the present invention are characterized in that the second layer is continuous and possesses a lower moisture permeability than the first layer.

In accordance with the above, the invention relates to a preparation containing active and/or auxiliary substances which has the aforementioned features, for time- and/or dose-controlled release of said substances, said preparation containing at least two layers (1, 2) in rolled-up or folded form.

The carrier layer (1) may either be covered along its entire length by an active agent-free matrix layer (2), but it may also have active agent-containing regions in longitudinal direction such that the active agent-containing and active agent-free regions alternate at distances. Furthermore, the carrier layer may in its longitudinal direction also possess regions with matrix layers containing different active and/or auxiliary substances.

Especially advantageous are such embodiments which have at least one continuous and largely moisture-impermeable layer. This layer too, may if it appears advantageous, contain active substances or auxiliary substances, or both at the same time.
Via this moisture-impermeable layer the diffusion of water or body fluids - and the degradation of the layer by erosion, dissolution, etc., associated therewith - takes place at a slower pace than is the case in the active substance-containing layers, so that in the latter the

degradation of the layer and thereby the release of active substance starts earlier.

A further embodiment provides for at least one of the layers (2) of the laminate to be soluble or erodible in body fluid, and for another layer (1) to be less soluble or more difficult to erode, or even insoluble or non-erodible.

It is to be noted here that there exists an interaction between solubility or degradability on the one hand and the thickness of the material on the other. Thus, a largely insoluble material may be configured comparatively thin, while on the other hand in the case of moisture-permeable, more readily soluble, erodible or biodegradable materials, the layers must be of a correspondingly greater thickness.

Usually, the active agent concentration is the same everywhere along the longitudinal extension of the active agent-containing layer. However, it may be of advantage for the concentration of the active substance or active substances to be different in relation to the longitudinal extension of the active substance-containing layer(s), as according to a preferred embodiment of the invention. In this case, the differences in concentration may preferably be configured in the form of a concentration gradient, or in the form of an otherwise variable concentration profile.

In addition, one may make use of the feature of at least one layer being pressure-sensitive adhesive.
The active substance layer, also called matrix, may over its entire length have uniform thickness; in this case the width of said layer may vary along its extension in longitudinal direction. The result of this is the so-called width profile.

In one embodiment of the invention, in the case of a rolled-up laminate, the outer layer may be active agent and/or auxiliary agent-containing.

However, in another embodiment, it is also possible for a pressure-sensitive adhesive, liquid-soluble active substance layer to be provided on the inside of the winding so that thereby the largely active agent-free carrier layer prevents a premature release of active agent. When this spirally wound up preparation is exposed to a body fluid, the active substance-containing adhesive dissolves and partially unrolls the system. In accordance with the surface area that has been exposed at any given moment, active substance can then enter from the said layer into the body fluid by diffusion or solution. Thus, the release profile is controlled by the geometry of the active substance layer. In this process, the slow unrolling of the system successively exposes new active substance-containing surfaces, so that the release profile results from the layer geometry and the speed of unrolling.

In a further embodiment of the invention, provision may be made for the measure of arranging the active substance-containing layer on the outside of the spiral, whereas the inner winding is formed by the carrier layer.

An advantage of this embodiment is the initial dose provided by the active substance-containing outer winding.

A further embodiment of the invention provides for layer regions with active and/or auxiliary agents to be present which differ in terms of their ingredients and/or their solubility, adhesive power or erosion properties.
As a consequence, the release profile can additionally be further modulated, and, in particular, can be imprinted in a dose-modulated manner in the process. The control of

active substance release in this embodiment is accomplished in chronologically successive "pulses" by exposure of different surfaces comprising different active and auxiliary substances.
The invention thereby enables the release of different active agents with differing active substance kinetics. For example, the active substance layer can be formed by two regions carrying different active substances, one of said regions providing pulsed release and the other region enabling a continuous release of active substance.

The invention further comprises the possibility of winding the laminate, which is present in sheet-like form, on a winding core, which is removed after completion of the winding, so that a central recess results. This recess may be 0.5 to 30 mm in diameter, preferably 1 to 10 mm, more preferably 2 to 5 mm.

Furthermore, the winding core may also remain in the system as a component of the preparation; said winding core may be compact or hollow, i.e. configured as a ring, contain an active substance or be configured to be largely free of active substance. In addition, the width of the winding core may exceed the maximum width of the laminate. The diameter of said winding core is 0.5 mm to 30 mm, preferably 1 to 10 mm, and more preferably 2 to 5 mm.

The active substance release may be effected by diffusion and/or dissolution of the active substance from an active substance layer which is largely insoluble in acid and/or basic environment, or by degradation or dissolution of an active substance layer which is soluble in acid and/or basic environment.

To produce a preset active substance release profile, it may be advantageous for the thickness of a layer to be in

the range of between 1 µm and 500 µm, preferably between 5 µm and 150 µm, more preferably between 10 µm and 30 µm. The width of an active agent-containing layer may be in the range between 1 mm and 50 mm, preferably between 1 mm and 30 mm, more preferably between 10 mm and 30 mm.
It may in addition be of advantage for the purposes of the present invention that the area of the active substance layer, relative to the carrier layer, be in the region of between 1 and 99%, preferably between 10 and 80%, more preferably between 30 and 70%. The unwound length of the total system may advantageously be in the range of between 5 mm and 300 mm, preferably between 10 mm and 200 mm, more preferably between 10 mm and 50 mm.

With respect to the release profile, such embodiments of the invention are particularly preferred as are characterized by a linear course of release. Furthermore, those embodiments are especially preferred which have the capability of releasing an initial dose. The initial dose may be provided, for instance, by means of an active substance-containing outer winding.

It may also be of advantage if the rolled-up or folded preparations of the invention are provided with additional cover layers at those sides which correspond to the longitudinal sides of the respective layers. This creates a protection against the attack of water or body fluids. Preferably, said lateral cover layers comprise largely moisture-impermeable materials.

For the manufacture of suitable administration forms, the rolled-up or folded preparations of the invention are preferably imbedded in a substrate which may consist of a substance soluble in acid or basic medium, for example in the form of hard or soft gelatine capsules.

A use of the preparation according to the invention is provided for the controllable release of active substance in the gastric juice region. However, it may also be provided for the controllable release of active substance in the gastrointestinal tract, especially in the small intestine. Such difference depends, in a manner known per se, on the pH value of the body fluid in the acid region of the stomach on the one hand, or on the other in the neutral or basic region of the small intestine. Preferably the preparation serves to attain a freely modulatable control and especially a linear control of the release of active substance. Finally, the release of active substance may also be provided for in the large intestine.

Finally, the preparation may be utilized for the controllable release of active agent and auxiliary agent, for instance in the form of a moulded article such as a suppository in the anal and vaginal region, or as an implant.

Suitable active agents are found in the active substance groups of the parasympatholytics (e.g. scopolamine, atropine, berlactyzine), the cholinergics (e.g. physostigmine, nicotine), the neuroleptics (e.g. chlorpromazine, haloperidol), the monoamine oxidase inhibitors (e.g tranylcypromine, selegiline), the sympathomimetics (e.g ephedrine, D-norpseudoephedrine, salbutamol, fenfluramine), the sympatholytics and anti-sympathotonics (e.g. propanol, timolol, bupranolol, clonidin, dihydroergotamine, naphazoline), the anxiolytics (e.g. diazepam, triazolam), the local anaesthetics (e.g. lidocain), the central analgesics (e.g. fentanyl, sufentanil), the antirheumatics (e.g. indomethacin, piroxicam, lornoxicam), the coronary therapeutics (e.g. glycerol trinitrate, isosorbide dinitrate), the estrogens, gestagens and androgens, the antihistaminics (e.g. diphenhydramine,

clemastin, terfenadine), the prostaglandin derivatives, the vitamins (e.g. vitamin E, cholecalciferol), the antitumor agents and the cardio-active glycosides such as, for instance, digitoxin and digoxin.

As components comprised in the base material of the layers containing active substance may be utilized polymers such as polyisobutylene, esters of polyvinyl alcohol, polyacrylic, polymethacrylic and polymethyl-methacrylic acid and their derivatives, natural rubber, styrene, isoprene and styrene-butadiene polymerisates or silicone polymers, resin components such as saturated and unsaturated hydrocarbon resins, derivatives of abietyl alcohol and ß-pinene, softeners such as phthalic acid ester, triglycerides and fatty acids, as well as a number of further substances known to those skilled in the art.

For the layers configured as insoluble, a plurality of materials are in principle suitable, especially those acceptable for pharmaceutical products: polyvinyl alcohol, styrene-diene block copolymers, polyurethanes, polyvinyl chloride, polymethacrylates, polyacrylate, polymethyl acrylate, polymethyl methacrylate and derivatives, polyolefin as well as polyester, to mention but a few examples.

A process for manufacturing a preparation according to the invention is characterized by the steps listed in Claim 20. One embodiment of the process provides that to achieve a desired release program after application parts of the active and/or auxiliary substance layer in the longitudinal extension of the laminate are removed or added. Also, further active layers may be laminated to the laminate. Finally, an ultimate step of the process provides for the preparation to be embedded in a substrate.

Further details, features and advantages of the invention will become apparent from the following illustration of some embodiment examples schematically represented in the drawings.
Figures I a/b, Figure II a-g, Figures III and IV, Figure V a/b as well as Figures VI a/b show, in side view or in plan view, preparations according to the invention in a substrate containing these preparations.

The embodiment according to Fig. Ia shows a pressure-sensitive adhesive water-soluble active substance layer (2) on the inside of the winding, with the active substance-free carrier layer (1) preventing a premature release of active agent.
When this rolled-up preparation is exposed to body fluids, the active substance-containing adhesive dissolves and partially unrolls the systems, during which process active substance can enter, by diffusion or solution, from the layer (2) into the body fluid in correspondence with the surface area which has been disposed at a given moment. The release profile is thus controlled by the geometry of the active substance layer, the slow unrolling of the system successively exposing new active substance-containing surfaces, and the release profile resulting from the layer geometry and the speed of unrolling.

According to Fig. 1, the active substance-containing layer (2) is positioned on the outer side of the spiral whereas the inner winding is formed by the carrier layer. The advantage of this embodiment is the initial dose provided by the active agent-containing outer winding.

Figures II a, d, f, g, each show different embodiments of the partially unrolled system in plan view, while Figures II d, c, e show the embodiments in side view.

The system according to Fig. II a, b enables a temporally pulsed active substance release, while embodiments II d, e result in a modulated swelling or deflation of the release. Fig. II f relates to an embodiment providing a slow rise or drop in active substance. Fig. II g shows a different embodiment providing a constant active substance release, as known in pharmaceutics as a release of zero order.

The invention moreover permits the release of different active substances with different release kinetics. For example, Figure III shows an embodiment of this kind with the active substance layer being formed by two different regions (Fig. III, 2, 3) carrying active substances; region 2 in the instant case providing a pulsed release whereas region 3 enables a continuous release of active agent.

The embodiment in Fig. IV also comprises two regions: Region 2 is configured as active substance-containing, water-soluble adhesive, region 3, by contrast, as largely active substance-free or active substance-containing, but water-insoluble sealing region. The water-insoluble sealing region at the edges has a protective function since without this barrier active substance would, in the unrolled state, be prematurely released via the sides. The stability of the rolled-up preparation in this case is produced by the centrally applied adhesive in region 2, and only insignificantly by the barrier region. Here, it is ensured that the active substance is released exclusively via the unrolled, exposed areas. However, it is also feasible that for this purpose the end faces of a rolled-up system are adhesively bonded or sealed such that the bond or seal is slowly soluble.

Furthermore, it may be of advantage to include a further layer in the system, which for example takes over the pressure-sensitive adhesive properties.

Fig. V a, d shows an example of such an embodiment, in plan and side view, respectively. The said layer may be adapted so as to contain active agent or be free of active agent, and may be soluble or insoluble in water.

Fig. VI a, b shows in plan and side view, respectively, the preparation of the invention in a substrate 5 containing said preparation, the substrate consisting of a substance soluble in acidic and/or basic medium.
Such configuration of the invention may be advantageous if the carrier layer is erodible or soluble in water.
Moreover, the pressure-sensitive adhesive layer can be insoluble.
Figure VI shows the substrate 5 enveloping the preparation of the invention in plan view (VI a) and in side view (VI b), respectively. The preparation can be configured as hard or soft gelatine capsule, but may also be present in form of a suppository.

The invention can be realized in an uncomplicated manner and represents an optimal solution to the task posed at the outset.

C L A I M S

1. Preparation containing active and/or auxiliary substance(s), for the time- and/or dose-controllable release of said substances, comprising at least two layers (1, 2) in rolled or folded shape, characterized

a) in that the first layer contains at least one active or auxiliary substance, is continuous at least in sections thereof, that at least one of the parameters thickness, width and concentration of the active and/or auxiliary substance of this layer is not constant, and that

b) the second layer is continuous and possesses a lower moisture permeability than the first layer.

2. Preparation according to Claim 1, characterized in that in the longitudinal direction of the carrier layer (1), active substance-containing regions of a matrix layer (2) alternate at distances with active substance-free regions of the carrier layer (1).

3. Prepararation according to Claim 1 or 2, characterized in that it comprises at least one continuous and substantially moisture-impermeable layer.

4. Preparation according to Claim 3, characterized in that the substantially moisture-impermeable layer contains one or more active substances and/or auxiliary substances.

5. Preparation according to one or more of the preceding Claims, characterized in that at least one of the layers (2) of the laminate is soluble or erodible in body fluid, and another layer (1) is less readily soluble or more difficult to erode, or is even insoluble or non-erodible.

6. Preparation according to one or more of the preceding claims, characterized in that the concentration of the active substance or of the active substances varies in respect of the longitudinal extension of the active substance-containing layer(s), preferably in the form of a concentration gradient or an otherwise variable concentration profile.

7. Preparation according to one or more of the preceding claims, characterized in that at least one layer, in particular the matrix (2), is pressure-sensitive adhesive.

8. Preparation according to one or more of the preceding claims, characterized in that in the spirally rolled-up laminate the outer layer (2) contains active and/or auxiliary substances.

9. Preparation according to one or more of the preceding claims, characterized in that in the spirally rolled-up laminate the inner layer (2) contains active and/or auxiliary substances.

10. Preparation according to one or more of the preceding claims, characterized in that one layer has regions with active and/or auxiliary substances, which regions differ in terms of their solubility, adhesive power or erosion properties.

11. Preparation according to one or more of the preceding claims, characterized in that if it is configured in form of a winding, it comprises a winding core which consists of material which is optionally soluble or insoluble in body fluid.

12. Preparation according to one or more of the preceding claims, characterized in that in the centre of the winding

there is formed a tube-like recess of at least 0.5 mm in diameter.

13. Preparation according to one or more of the preceding claims, characterized in that the preparation effects a linear release of active substance.

14. Preparation according to one or more of the preceding claims, characterized in that the preparation effects the release of an initial dose.

15. Preparation according to one or more of the preceding claims, characterized in that those sides of the spirally rolled-up or folded preparation which correspond to the longitudinal sides of the respective layers are provided with additional cover layers, said cover layers preferably containing substantially moisture-impermeable materials.

16. Preparation according to one or more of the preceding claims, characterized in that the preparation is embedded in a substrate (5) which preferably consists of a substance that is soluble in acidic or basic environment.

17. Use of the preparation, for example in the form of a rolled-up formed article for the controlled release of active and/or auxiliary substance in the anal or vaginal region, or as an implant.

18. Use of the preparation for oral application for the purpose of releasing active and/or auxiliary substances in the gastrointestinal tract, especially in the small intestine or the large intestine.

19. Use of the preparation for oral application for the purpose of releasing active and/or auxiliary substance in the region of the gastric juice.

20. Process of manufacturing a preparation according to the invention, characterized by the steps:

- providing a carrier layer (1),
- coating said carrier layer (1) with at least one active layer (2) containing active and/or auxiliary substance, thus forming a laminate,
- drying of the laminate,
- applying along the longitudinal extension of the laminate a thickness and/or width profile which can be modulated as required for achieving predeterminable release kinetics,
- forming an application form from the preparation by rolling or folding,
- final packaging.

21. Process according to Claim 20, characterized in that to achieve a desired release schedule following application parts of the active and/or auxiliary substance layer (2) are removed or added in the longitudinal extension of the laminate.

22. Process according to Claim 20 or 21, characterized in that further active layers (3, 4) are laminated to the laminate.

23. Process according to one or more of Claims 20 to 22, characterized in that the preparation is embedded in a substrate (5).

ABSTRACT

A preparation containing active and/or auxiliary substance(s) for the time- and/or dose-controllable release of said substances, comprising at least two layers (1, 2) in rolled or folded shape, is characterized in that a) the first layer contains at least one active or auxiliary substance, is continuous at least in sections thereof, that at least one of the parameters thickness, width and concentration of the active and/or auxiliary substance of this layer is not constant, and b) in that the second layer is continuous and possesses a lower moisture permeability than the first layer.

FIG.1

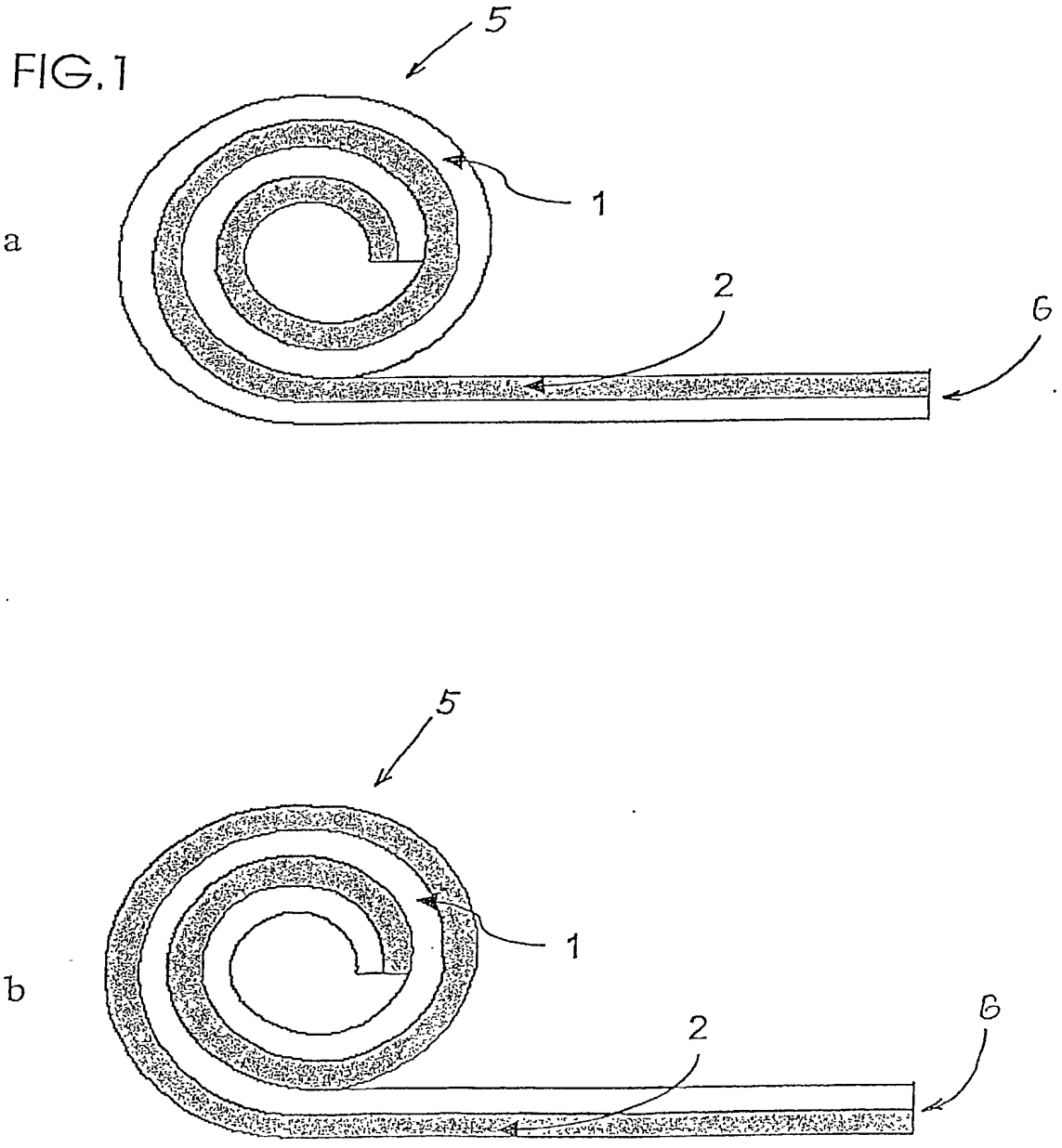


FIG.2

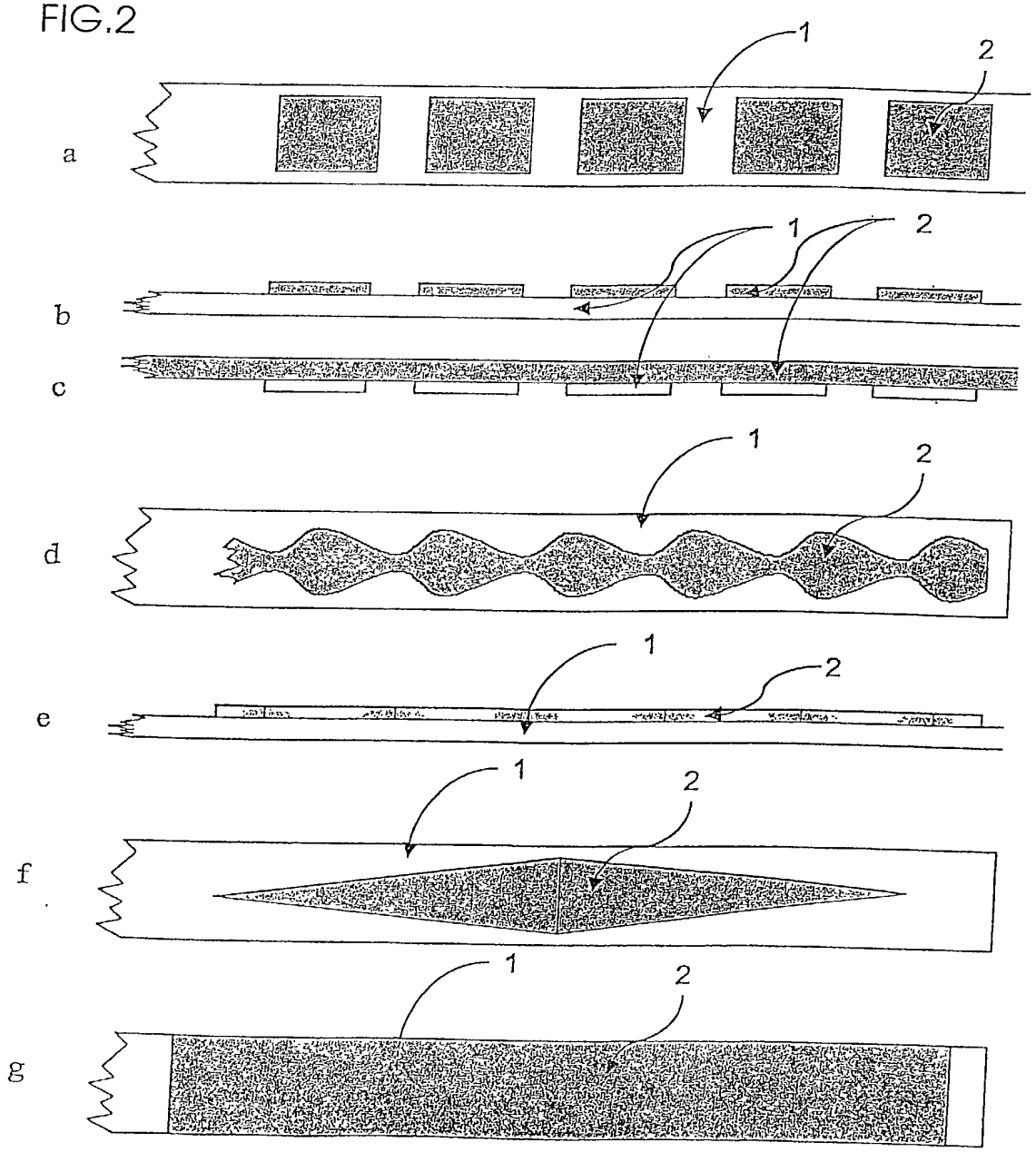


FIG.3

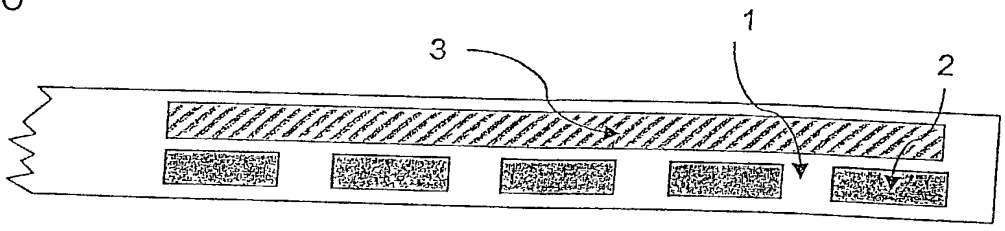


FIG.4

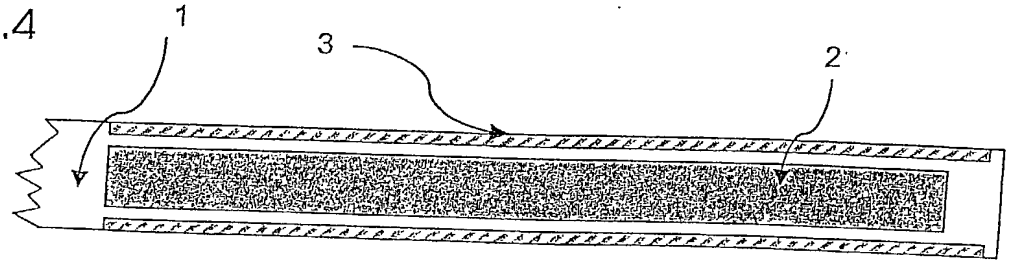


FIG.5

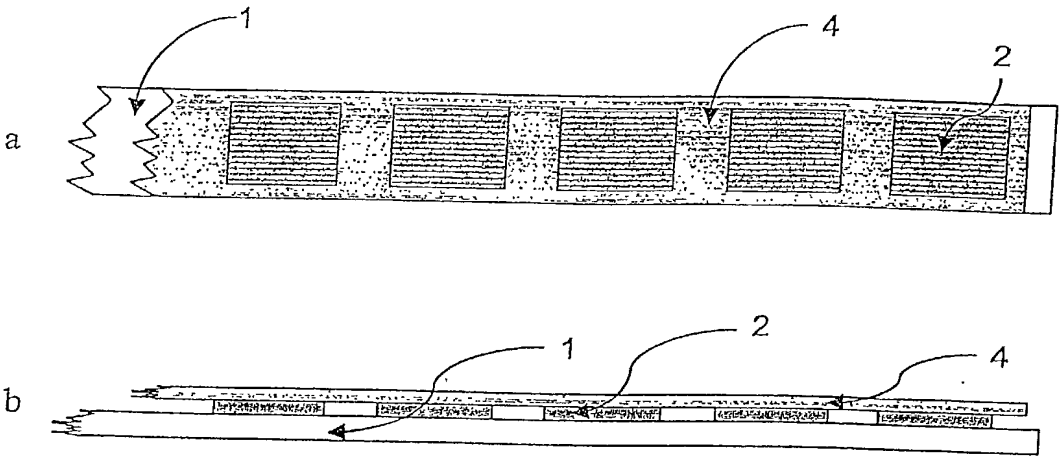
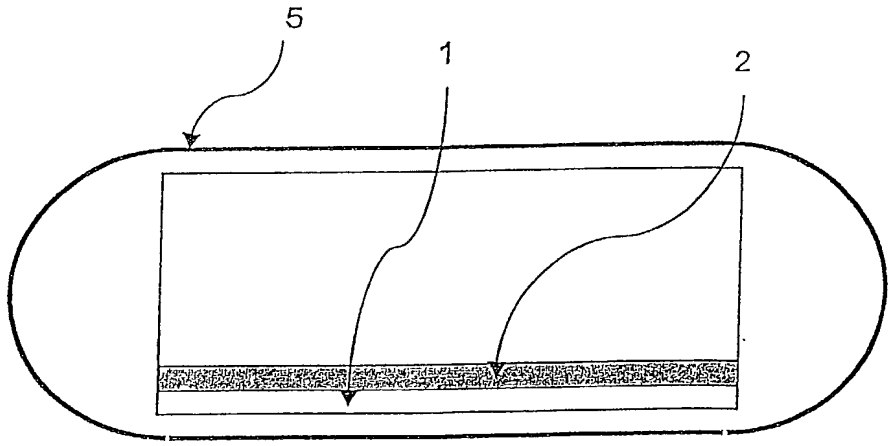
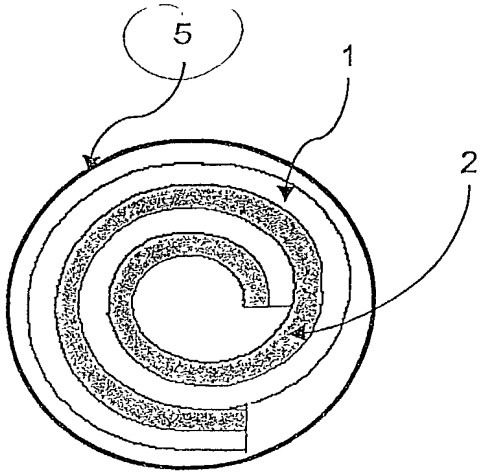


FIG.6



a



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COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT AND DESIGN APPLICATIONS

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Insert Title: PREPARATION CONTAINING ACTIVE AND/OR AUXILIARY SUBSTANCES, WITH CONTROLLABLE RELEASE OF SAID SUBSTANCES, AS WELL AS ITS USE AND MANUFACTURE

Fill in Appropriate Information - For Use Without Specification Attached:

the specification of which is attached hereto. If not attached hereto,
the specification was filed on March 29, 2002 as
United States Application Number ;
and amended on March 29, 2002 (if applicable) and/or
the specification was filed on September 16, 2000 as PCT
International Application Number PCT/EP00/09061 ; and was
amended on October 8, 2001 (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representative or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Insert Priority Information: (if appropriate)

Prior Foreign Application(s)			Priority Claimed	
199 46 822.2 (Number)	GERMANY (Country)	September 30, 1999 (Month/Day/Year Filed)	☒ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional applications(s) listed below.

Insert Provisional Application(s): (if any)

(Application Number) (Filing Date)

(Application Number) (Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More than 12 Months (6 Months for Designs) Prior to the Filing Date of This Application:

Insert Requested Information: (if appropriate)

Country	Application Number	Date of Filing (Month/Day/Year)

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Insert Prior U.S. Application(s): (if any)

(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)
(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)

I hereby appoint the practitioners at **CUSTOMER NO. 2292** as my attorneys or agents to prosecute this application and/or an international application based on this application and to transact all business in the United States Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the practitioners, unless the inventor(s) or assignee provides said practitioners with a written notice to the contrary:

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MAILING ADDRESS (Complete Street Address including City, State & Country)		

*DATE OF SIGNATURE